

THE TREATMENT OF SCARLET FEVER WITH
SPECIFIC ANTITOXIC SERUM.

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THE TREATMENT OF SCARLET FEVER WITH SPECIFIC ANTITOXIC SERUM.

As a basis for the proper interpretation of the therapeutic value of Scarlet fever streptococcus antitoxic serum it is necessary to have a clear understanding of the nature and clinical course of the disease.

Zingher¹ gives us the following definition:-

"A local disease of the nasopharyngeal mucous membrane caused by certain specific strains of the haemolytic streptococcus. A soluble toxin is produced locally which is absorbed into the system and gives rise to the rash and constitutional symptoms. The toxin paves the way for the secondary invasion of the system by the specific haemolytic streptococcus and other organisms present in the bacterial flora of the nasopharyngeal cavities."

Such secondary invasion of the tissues, whose power of resistance is lowered by the specific toxæmia, gives rise to many of the complications associated with the disease.

The above conception of Scarlet Fever is now used as the foundation stone for the rational specific therapy of a disease which beforehand was treated purely on symptomatic grounds.

The etiological relationship between certain specific/

specific strains of the haemolytic streptococcus and Scarlet fever has been established through the work of Tunnicliff², Bliss³, Gordon⁴, Dochez⁵, Dick and Dick⁶, Zingher⁷ etc., and the Dicks brought out the fact that these organisms produced a toxin which, when injected into horses, produced an antitoxic serum for which favourable results have been claimed.

The belief in the part played by Streptococci in the causation of Scarlet fever is no recent knowledge, for Klein⁸ in 1886 described the *Streptococcus Scarlatinae* and antistreptococcal serum was used in the treatment of Scarlet fever by Marmorek⁹ in 1895.

He immunised animals with polyvalent strains of the haemolytic streptococcus isolated from throats of Scarlet fever cases, but the results obtained were disappointing.

Moser¹⁰ in 1902 prepared antistreptococcal serum by immunising horses with haemolytic streptococci isolated from the throats of malignant cases of Scarlet fever.

Favourable results from the use of this serum were reported by Schick,¹¹ but, owing to severe serum reactions, it fell into disuse.

Certain later types of polyvalent antistreptococcal serum have been used with varying success in purely septic cases, when directed specially against the septic manifestations.

Goodall¹² /

Goodall¹² confirmed the opinion of Compston¹³ who used a polyvalent antistreptococcal serum.

He believed that 50 ccm. of polyvalent anti-streptococcal serum, injected early in septic cases, produced marked improvement.

Claud Ker,¹⁴ however, had a poor opinion of these sera and in his hands their use in septic cases had been disappointing.

In some cases an almost miraculous recovery occurred and he attributed that to the serum being prepared from a strain of streptococci which was identical with that causing the worst features of the illness.

Ker was the first to show that some of these sera possessed either no antitoxic titre at all, or so little that they would not produce a positive Schultz-Charlton reaction.

Harries¹⁵ expresses his opinion of these sera in the following way:-

"My own experience of polyvalent sera is extensive and my impressions are that, if given early in septic cases, they have had a favourable effect upon the septic process. If given late or in small doses (less than 50 ccm.) they are useless."

Weisbecker¹⁶ in 1897, led by the fact that one attack of Scarlet fever renders most people immune, treated the disease with the serum of convalescent Scarlatinal/

Scarlatinal patients.

His results were not favourable.

This work was taken up later by other workers and Bernbaum¹⁷ at Herman Kiefer Hospital, Detroit, U.S.A. reported success with convalescent serum in severe cases.

He later stressed the importance of giving the serum early and using large doses. (50 - 100 ccm.).

The practical difficulty of getting convalescent serum in bulk renders its use limited.

Zingher and others have used citrated whole blood from convalescents in doses up to 250 ccm., and Claud Ker has described a genuine toxic case of Scarlet fever treated in this manner. Death appeared certain before injection, but, following it, steady improvement developed after 45 ccm. of citrated whole blood from a convalescent on the twenty-fourth day of disease.

Birkhaug¹⁸ also reports upon the use of serum withdrawn from convalescents during the third to fifth weeks of disease. A dose of 15 - 85 ccm. was injected intramuscularly during the first seven days of disease.

He concludes that convalescent serum causes rapid improvement in the toxæmia with slight fall in temperature and pulse, but has no effect upon the rash or incidence of septic complications.

Dochez and others have demonstrated that the haemolytic/

haemolytic streptococcus from Scarlet fever throats is morphologically and culturally similar to other strains of the haemolytic streptococcus, but serologically specific - being only agglutinated by the specific antiserum.

Dochez¹⁹ immunised horses with strains of this specific haemolytic streptococcus, described by Dick and Dick,⁶ and obtained a serum which blanchered locally the rash of Scarlet fever.

This serum, produced by the injection of live virulent cultures into horses, was claimed to possess antibacterial as well as antitoxic properties.

A description of thirty-one cases of Scarlet fever treated with Dochez' serum is given by Birkhaug¹⁸ who used the serum intramuscularly in average dose of 40 ccm. in cases within the first four days of disease.

A local blanching test was performed in seventeen cases, before the therapeutic dose was given, and found to be positive in all.

An effort was made to standardise the dose necessary to effect clinical improvement in moderately severe cases.

The required dose was found to range from 10 - 80 ccm.

Marked improvement in toxaemic symptoms was noted immediately after the injection of serum, together with/

with blanching of the rash in 12 - 24 hours.

He claims that the incidence of septic complications was low in cases treated prior to the fourth day of disease, but that cases with septic complications yielded slowly to Dochez' serum.

He was of the opinion that Dochez' serum, contrasted with convalescent serum, was more favourable.

Samples of blood taken six hours after giving 40 ccm. of Dochez' serum caused a positive Schultz-Charlton reaction.

Insufficient dosage was the cause of lack of improvement in some cases.

He says that:-

"When serum was given later than the fourth day or in presence of already existing septic complications - the results are not conclusive."

He emphasises the necessity of giving serum at the earliest possible moment and points out that the high incidence of serum sickness may be obviated later by purification and concentration of the serum.

Thenebe²⁰ records his results from the treatment of cases of Scarlet fever by the intravenous injection of Dochez' unconcentrated serum.

No untoward results occurred from these injections, though in some cases serum sickness was fairly severe and he points out that, by this route, immediate maximum concentration of the serum in the blood-stream was /

was obtained.

Thus a smaller therapeutic dose is necessary when given intravenously than when administered by the intramuscular route.

He records a critical fall of temperature with rapid fading of the rash and states that:-

"The incidence of complications and sequelae seems to be lessened after Dochez' serum.

Complications, once started, are not affected materially by serum. This is due to organisms or their toxins being lodged in other foci, e.g. glands, ears etc., besides the original focus, viz., nasopharynx. It seems feasible that this extension may be averted by an early, adequate dose of serum. If the inflammatory process is well advanced and a mixed infection present, the process is not affected by the addition of serum."

He concludes that antiscarlatinal serum is a valuable therapeutic agent in the treatment of Scarlet fever and advocates that cases of streptococcal septicaemia should be given the benefit of Dochez' serum, administered in large doses, to combat the toxæmia and to permit the probable bactericidal properties of the serum to function.

Blake and Trask²¹ give a survey of their experiences in the treatment of Scarlet fever with Dochez' unconcentrated serum.

In/

In their preliminary report²² they state that antitoxin, when used early, appeared to effect a prompt cure as evidenced by a critical fall of temperature and pulse rate to normal, a rapid fading of the rash and prompt disappearance of toxaemic symptoms.

In support of this clinical observation it was shown in further reports²³ that the antitoxin in therapeutic doses promptly neutralised the toxin and established an excess of antitoxin in the blood.

In their investigations they distinguish between the effect of the serum on the specific toxaemia of Scarlet fever and the septic aspect of the disease.

They treated fifty-seven uncomplicated cases, forty-eight complicated cases and seven cases of post Scarlatinal sepsis.

The following are their conclusions:-

"Antitoxin is a specific and effective cure for simple Scarlet fever; that it promptly cures the toxic phase of septic Scarlet fever, but doesn't affect the septic aspect of the disease. Even though it doesn't cure the septic aspect of the disease, it nevertheless benefits by freeing them of the toxaemia and so placing them in a better position to fight the sepsis. It shows no effect on septic complications after the toxaemia has subsided."

They insist on the early administration of serum, while the toxic phase is at its height and before the septic aspect becomes the dominant factor.

"Under/

"Under these circumstances a critical cure may be expected and the probability that subsequent complications will develop is small."

As to the question of dosage, they point out that the amount of antitoxic serum required varies with the size of the patient, the severity of the disease and the antitoxic content of the serum used. It also varies with the method of administration:- intravenous in contrast to the intramuscular route.

"The object in giving serum is to effect prompt neutralisation of toxin and to establish an excess of antitoxin in the blood till the patient has time to develop his own antibodies."

Park of New York first used Scarlet fever antitoxin in January 1924 and the serum used was that of Dochez. He found that the serum was not potent enough and the results were not striking.

Later he²⁴ gives us his observations when he used a serum of his own and a new type of that of Dochez.

Working at the Willard-Parker Hospital, New York in January 1925 he gave it to alternate patients and to severe cases by the intravenous route.

Most of the serum was not refined, but some was concentrated and the serum reactions with the latter he found were only 50% of those with the former preparations.

He believes that, as long as the rash remains, - antitoxin is indicated.

He agrees with other observers that antitoxin has little effect on septic complications already developed; but before their onset the serum appears to be of service in preventing them.

He ascribes this property to the raising of the resistance, local and general, so as to prevent invasion of the tissues by streptococci.

These streptococci may be the specific strains associated with Scarlet fever or other forms.

His conclusions on the therapeutic value of serum are as follows:-

" 1. Sera used by Moser produced the same therapeutic results as that of Dochez, but, owing to lack of methods of testing their potency, some were probably very weak and account for the disappointing results.

2. Serum should be given in sufficient dose at earliest possible moment. When thus given the results in most cases are strikingly favourable.

3. The early use of serum probably frequently prevents the development of complications.

4. Serum is useless after rash has gone and has no effect on late septic complications.

5. In mild cases it should be given by the intramuscular route, but in severe cases it should be given by the intravenous route.

6. In mild cases one dose is enough, but in severe cases the dose should be repeated if necessary in 12 - 24 hours.

7. It is doubtful if serum should be given in very mild cases.

8. A unit should be adopted so that results from different doses can be compared."

He draws attention to the probability that a few failures in serum treated cases may be due to the fact that some toxic cases are caused by different strains of the haemolytic streptococcus which produce toxin which is not neutralised by the serum.

He also raises the question as to whether a serum with antibacterial as well as antitoxic properties is superior in action to a purely antitoxic serum.

Gardner Robb²⁵ speaks very favourably of his results with antiscarlatinal serum.

Serum used was that of Dochez, some being unrefined, which he used in doses of 30 - 40 ccm., the remainder being concentrated and used in doses of 10 - 20 ccm.

A third type of serum used in his series of one hundred and forty cases was the concentrated Scarlet fever streptococcus antitoxin of Messrs Parke Davies and Co.

He administered the serum to cases of more than average severity within the first three days of disease.

"In/

"In such early cases" he states "The attack has been completely aborted, desquamation and complications prevented or greatly diminished, so much so that quarantine period could be reduced by some 50%."

"As result of the experience I have had with this treatment I am very hopeful that we have now a remedy which gives promise of great usefulness and, if the estimate we have formed is found to be the general experience, we may look for a reduced case mortality and a great reduction in serious complications and sequelae of Scarlet. By the cutting down of the necessary quarantine period we may hope for much relief to strain which Scarlet fever puts on accommodation in fever hospitals. As a prophylactic this period should prove of great service."

He points out the difficulties of testing the potency of these sera owing to the lack of efficient tests on laboratory animals and draws attention to the danger of inferior sera of low potency appearing on the market.

Thus for obtaining the best results the two essentials are:-

- (1) Serum of high potency.
- (2) Early cases.

Harries,¹⁵ Medical Superintendent of Birmingham City Hospitals, used a preparation of Scarlet fever antitoxic/

antitoxic serum supplied by the Wellcome Physiological Research Laboratories and summarises his impressions of the treatment of seventy cases.

He reports very favourably on the action of this serum in two cases of toxic Scarlet fever treated with 80 ccm. and 40 ccm. respectively.

Injectations were given intramuscularly.

To other cases he gave 20 - 30 ccm. intramuscularly and was of the opinion that this was too small a dose for an unconcentrated serum and he later gave a minimum dose of 40 ccm.

He agrees with the favourable influence which serum has in reducing pyrexia, blanching the rash and counteracting the general toxæmia of the disease.

In his experience antitoxic serum has a beneficial effect in lessening complications, but has no direct action upon septic complications already present.

In 1924 Dick and Dick²⁶ reported a Scarlet fever antitoxin produced by immunising horses with gradually increasing doses of Scarlet fever streptococcus toxin. This serum was concentrated by the usual methods.

Up to that time sera for treatment of Scarlet fever had been produced by immunising horses with living cultures of the haemolytic streptococcus.

The Dicks believe that the beneficial action of the serum is probably due to the antitoxin.

Prior to 1924 no attempt had been made to concentrate/

concentrate any of the sera then in use, and it is now generally recognised that concentrated sera cause fewer and less serious reactions than the unconcentrated varieties.

"The fact that Scarlet fever antitoxin may be employed in the concentrated form makes its use in the treatment of Scarlet practical."

Owing to the fact that the severity of Scarlet fever varies from year to year and that the disease in one locality may be of a milder type than that in another place at the same time; they stress the necessity for adequate controls before determining the value of any therapeutic measure in Scarlet fever.

They used as control cases of Scarlet fever occurring in Chicago at the same time as antitoxin was being employed.

In their series of cases²⁷ antitoxin was only given to the more severe types of disease.

They draw attention to the point that, owing to the Death rate from Scarlet fever having remained very low for a number of years, if a serum is to have any value as a routine therapeutic measure it must have a beneficial effect upon the frequency of complications.

Their best results were obtained when a large dose was given early in the disease.

They took as their therapeutic dose the amount of antitoxin which would neutralise 20,000 skin test doses /

doses of Scarlet fever toxin.

In their conclusions they state that:-

" 1. The results in the antitoxin series and the control series indicate that concentrated Scarlet fever antitoxin, injected intramuscularly, blanches the rash, lowers the temperature and improves the general condition of many Scarlet fever patients.

2. If the antitoxin be given early in the disease, the course of the disease is shortened and the incidence of complications and sequelae is greatly diminished.

3. One therapeutic dose in moderately severe cases is enough."

Results of a further series of one hundred cases with controls, by the same authors,²⁸ are classified as follows:-

"A study of this series leaves no doubt that antitoxin shortens the course of disease and reduces the number and severity of complications and sequelae."

Ferry, Bernbaum and Crissman²⁹ record their results with a serum prepared by injecting both live virulent organisms and toxic filtrates. The serum is thus antibacterial as well as antitoxic and by some is believed to be superior to a purely antitoxic serum.

An article by Williams,³⁰ based on experiments of workers in New York City Health Laboratories would seem/

seem to bear out this idea.

The serum was concentrated by the usual globulin method and found to neutralise 20,000 skin test doses of toxin per ccm. and to produce a positive Schultz-Charlton reaction.

(According to the Dicks²⁷ they consider a therapeutic dose to be one which will neutralise 20,000 skin test doses of toxin.)

Twenty-five of the most severe cases of Scarlet fever in the Herman Kiefer Hospital, Detroit, were treated with 10-20 ccm. of this serum intramuscularly as soon as possible after admission.

"The comparison of these cases with those treated during the past two years with convalescent serum speaks very favourably for the antitoxin."

A record of one hundred and thirty severe and moderately severe cases of Scarlet fever treated with concentrated antitoxin, prepared according to the methods of Dick and Dick, is given by Anderson and Leonard.³¹

The serum used neutralised 20-30,000 skin test doses of Scarlet fever toxin per ccm. and that was the highest concentration they were able to get.

Their average dose of antitoxin was an amount equivalent to 184,000 skin test doses of toxin, i.e. almost ten times as strong as that used by Dick and Dick.

They/

They treated, with the same type of serum, cases of Scarlet fever in institutions in three different States of U.S.A. to disprove the suggestion that antitoxin prepared in one locality is not specific for the disease in other districts.

Their results led them to believe that the antitoxin used was specific for the various types of Scarlet fever.

Of the one hundred and thirty cases treated with antitoxin 4.6% developed complications, while in eighty-four mild cases used as controls (not receiving serum treatment) 28.6% had complications.

They consider an effective therapeutic dose to be one which will neutralise 200,000 skin test doses of Scarlet fever toxin.

In comparing the serum and non-serum cases they find the following results:-

"By the use of antitoxin we are able to obtain a more rapid subsidence of toxæmia, more rapid fading of the rash, more prompt return to normal of mucous membranes and a reduction in number and severity of complications.

The patients look and feel better and are more comfortable."

Cushing³² records his observations at the Alexandra Fever Hospital, Montreal - 1925-26.

This worker gives us the largest series of cases yet/

yet recorded.

He had a total of five hundred cases of Scarlet fever treated with antitoxic serum obtained from different sources.

Some was prepared by the Dick method, some by Dochez' method and some by a combination of these.

He found that the action of various preparations of serum differed only in degree, the effects varying according to strength and concentration of serum.

As controls he used his statistics of the same hospital for the previous year, taking a total of 1073 cases of practically the same clinical type of Scarlet fever.

The usual dose of serum was 10 ccm. given intramuscularly at the earliest possible moment and was only rarely repeated.

In a few toxic and septic cases it was given intravenously.

His 'modus operandi' was to give serum to every definite case of Scarlet fever unless of a very mild type.

He gives the following data to demonstrate the effect of antitoxic treatment of Scarlet fever upon the case-mortality from the disease:-

"At the Alexandra Hospital the mortality for Scarlet fever always used to be over 5%, but has been falling in recent years. In 1923 it was 3.25% and/

and in 1924, when convalescent serum was used in serious cases, 2%. Since the general use of antitoxin there have been eight hundred cases with ten deaths or 1.2%. None of the deaths, however, was due to Scarlet fever alone, among the cases treated with serum, but the cause of death was some intercurrent disease."

13% of his cases developed serum rashes.

He gives us the following conclusions in his summary:-

"1. Scarlet fever antitoxin is a specific remedy which cuts short the fever and relieves all its early manifestations.

2. It lessens the number and severity of complications and lowers the mortality of the disease.

3. Serum should therefore be given as early as possible in every case; dose being regulated by the severity of the case. Dose should be repeated if first dose is inadequate."

Benson and Maciver³³ record their observations on one hundred and seven cases of simple Scarlet fever treated with intramuscular injections of concentrated Scarlet fever antitoxin, with one hundred and seven control cases.

The authors' conclusions are stated in the following terms:-

"1. The administration of antitoxin within the first/

first forty-eight hours of the disease has a very favourable influence on the specific toxaemia of Scarlet fever.

In relieving the more urgent symptoms of the acute stage it undoubtedly renders the patient more comfortable.

2. There are indications that the liability to subsequent complications is diminished.

3. The administration of Serum, even on the first day of illness, apparently does not act as an absolute safeguard against the subsequent development of complications of septic type in convalescence."

They found that this serum, administered to two cases of septic Scarlatina on the second and third days of illness respectively, failed to influence the course of the disease.

In the treatment of the toxic type of Scarlet fever they advocate the giving of the serum preferably by the intravenous route at the earliest possible moment and to repeat the dose if necessary.

"The benefits of serum treatment" says J.E. Gordon³⁴ of Chicago "are best determined by treating a large number of cases within a short space of time."

His series of three hundred and seventeen cases were admitted to Hospital within a period of six months.

The cases include only those admitted on or before/

before the third day of rash, and were classified clinically as moderate, moderately severe and severe.

He gave serum to each alternate case on admission, selecting as far as possible the more severe cases for serum treatment and the milder ones as controls, thus making the test of the benefits of serum as severe as possible.

The serum used was a concentrated antitoxin prepared according to the Dick method and was given intramuscularly.

The majority of cases received only one dose, but in severe cases the dose was repeated in 12-24 hours.

The therapeutic dose of antitoxin was found to be such as to neutralise 250,000 skin test doses of Scarlet fever toxin.

He evaluates the antitoxic serum from the following standpoints.

1. The effect on general clinical course.
2. Complications following the initial febrile period.
3. Effect of serum on haemolytic streptococci in nose and throats.

Regarding these points he states that:-

"Scarlet fever antitoxic serum exerts a favourable and well marked effect in reducing the severity of the febrile stage of the disease, on course/

course and duration of fever, on extent and duration of skin lesions and on period of isolation.

There are fewer complications in patients receiving serum. A favourable effect on complications is evidenced by a lessened severity and duration as well as incidence.

Apparently the administration of antitoxic serum was associated with reduction of haemolytic streptococci in nose and throats of convalescents."

Bie, Larsen and Andersen³⁵ give a résumé of three methods of serum therapy in Scarlet fever.

1. A polyvalent antistreptococcal serum.
2. Serum of Scarlet fever convalescents.
3. Specific serum of *Streptococcus Scarlatinae*.

Each method, they say, has proved satisfactory, but the convalescent and specific sera give the best results.

The difficulty of obtaining sufficient quantities of suitable convalescent serum renders that method impracticable as a routine and the authors therefore recommend specific sera.

In a discussion³⁶ upon the Antitoxin treatment of Scarlet fever by the Royal Society of Medicine, Dr E.W. Goodall pointed out the difficulty of assessing the value of antitoxin treatment as the type of Scarlet fever was so mild, the case mortality being consistently/

consistently below 2% in London since 1910.

Thus other methods than the effect on case-mortality must be used to judge its merits.

He, personally, had only treated a small number of cases with serum and, though he was unable to speak with authority, his impressions were favourable.

At the same meeting Dr O'Brien reported results from various fever hospitals outside London. Concentrated serum in doses of 10-20 ccm. had been stated to have a definite beneficial effect in mild and moderate cases of Scarlet fever, but did not seem to touch the septic type of disease.

He then discussed the methods of standardising the serum.

He pointed out the close relationship between all the strains of the haemolytic streptococcus and suggested that other forms of streptococcal infection might be combated by Scarlet fever antitoxin.

In his opinion the problem of Scarlet fever is one of late morbidity and it is impossible to foretell what complications a mild case will develop later during convalescence.

Continuing the discussion Dr J.D. Rolleston emphasised the fact that, though Scarlet fever had a low case mortality in this country, it still had a high mortality rate in South-East Europe.

He/

He agreed that antitoxin should not be given to mild cases owing to the risk of serum sickness and resultant hypersensitiveness.

METHOD ADOPTED.

During the period October 1926 - April 1927 I have had the opportunity of treating with antitoxic serum, in the wards of the City Fever Hospital, Edinburgh, three hundred and sixty-five cases of simple Scarlet fever, nine cases of septic Scarlet fever and two cases of the toxic type of the disease.

I take this opportunity of expressing my grateful thanks to Dr W.T. Benson, Medical Superintendent, for permission to carry out the following work.

The practice I followed was to administer serum, at the earliest possible moment after admission, to every definite case of Scarlet fever of the simple type within the first three days of disease.

In my series I have included a few cases to whom serum was given on the fourth day of disease.

Such cases were of more than average severity and it was thought advisable to give them the benefit of serum therapy, though it is generally admitted that by this time patients have passed the stage of anti-toxin treatment proving beneficial.

Cases of a very mild type or of doubtful diagnosis were not chosen.

In my endeavour to obtain as large a number of cases as possible, within the prescribed period, for the/

the purposes of studying the effects of serum therapy, I was unable to secure adequate control cases admitted during the same months.

Thus for my control cases I studied the clinical course of a similar number of cases of definite Scarlet fever admitted to the City Fever Hospital, Edinburgh during the corresponding period October 1925 - April 1926.

I selected cases from the Hospital statistics bearing the same age period, the same clinical type, admitted to Hospital on the same day of disease and on a corresponding date to those in my series of serum treated cases.

Though it is recognised that Scarlet fever varies considerably in its severity from year to year, the control cases were selected to be comparable in every detail to those treated with serum and so this method of comparing and contrasting serum and non-serum treated cases is a reliable one, when a large number of cases is taken into account.

TYPE OF SERUM USED.

The preparation of serum used was a concentrated Scarlet fever streptococcus antitoxin derived from two sources:-

1. Messrs Parke Davis & Co.
2. Messrs Burroughs Wellcome & Co.

Based on the etiological relationship of certain specific strains of the Haemolytic Streptococcus to Scarlet fever, these sera are obtained from horses treated with gradually increasing doses of Scarlet fever streptococcus toxin and live virulent cultures of this organism recently isolated from the throats of those suffering from a severe type of the disease.

The process of concentration, in which the active globulin is separated from the other constituents of the serum, is carried out according to accepted methods and the sterility of the products is carefully controlled.

This serum globulin possesses both antibacterial and antitoxic properties and, following upon methods of testing its antitoxic titre, the serum of Messrs Parke Davis & Co. is claimed to contain in 10 ccm. or less an efficient therapeutic dose which is able to neutralise 500,000 skin test doses of Scarlet fever toxin.

The strength of the preparation of Messrs Burroughs /

Burroughs Wellcome & Co. is likewise tested and the recommended therapeutic doses are:-

10 ccm. for mild cases.

20 ccm. for severe cases.

20-50 ccm. for cases of a very severe type.

STANDARDISATION OF SERUM.

In the use of any antitoxic serum therapeutically one of the first considerations is to determine the antitoxic titre of a given quantity of that serum so that an estimate may be arrived at as to what constitutes an efficient therapeutic dose.

In the case of Diphtheria antitoxin, the most widely used of all our antitoxic sera, the methods of standardisation and titration are very definite and, with the help of tests upon such a laboratory animal as the guinea-pig, it has been possible to arrive at exact estimates of the unit of the Diphtheria toxin and its corresponding antitoxin.

We are less fortunately placed as regards the Scarlet fever toxin and antitoxin for, up to the present, laboratory animals have not given us the same invaluable help as in Diphtheria, and the stability of the toxins produced by the specific strains of the Haemolytic Streptococcus, now regarded as the causal agency of Scarlet fever, is not such a/
a/

a definite entity as that of the toxin of *Bacillus Diphtheriae*.

One is therefore faced with considerable difficulties in the standardisation of a Scarlet fever streptococcus antitoxin and, as yet, most of the available methods of testing its strength have been performed on human beings.

The unit of Scarlet fever toxin is termed the 'Skin test dose', which is defined as the minimum amount of a Standard Scarlet fever toxin which will produce a positive Dick test in a susceptible individual.

Any attempt at an explanation of the initial difficulties in procuring what is termed a standard Scarlet fever toxin and the finding of a suitable dilution of that toxin to constitute a skin test dose is beyond the scope of this paper, as also is any discussion upon the Dick test, first described by Drs George and Gladys Dick.

Corresponding to the unit of Scarlet fever toxin we have the unit of antitoxin which is described as that amount of antitoxin which will neutralise one hundred skin test doses of toxin.

Five methods of titrating Scarlet fever antitoxin have been elaborated, the first three of these are done on human volunteers and the last two upon animals.

The/

The following are the methods:-

1. Schultz-Charlton blanching test.
2. Toxin-antitoxin neutralisation.
3. Production of Passive Immunity.
4. Testing of power which Scarlet fever strepto-

coccus antitoxin has to protect rabbits against a lethal dose of a culture of the specific haemolytic streptococcus. It has been found that this property is not conferred upon such rabbits by normal serum, concentrated Diphtheria antitoxin or other antitoxins.

5. Skin neutralisation test in goats.

This method has been described by Wadsworth, Kirkbride and Wheeler³⁷ and these workers on the subject give us the following information:-

"A procedure for the standardisation of Scarlet fever antistreptococcus sera on the goat has been developed which appears to offer a more accurate, uniform, reliable and practical method of titration than do any of the methods on human subjects. Difficulty is to get sufficient number of goats and the fact that they become hypersensitive to horse-serum."

Of these five methods I have personally investigated the ones upon human volunteers and the following is a brief description of the methods used and the results obtained.

The serum used throughout the tests consisted of/

of samples taken from the stock used therapeutically in my series of cases.

METHOD 1.

The Schultz-Charlton blanching test as developed by Dochez and Sherman¹⁹ and Blake and Trask.³⁸

By the intracutaneous injection of a fixed quantity of serum in varying dilutions, in patients exhibiting a typical scarlatinal eruption, an attempt was made to determine the smallest amount of serum which would blanch locally that rash.

This amount of serum is designated the minimum blanching dose.

Only rashes within the first forty-eight hours of their appearance were chosen for testing, as it is generally agreed that after the second day the rash is definitely stained into the tissues of the skin and satisfactory blanching cannot be procured.

The amount injected in all cases was .2 ccm. and the dilutions used were as follows:-

1 in 1,000, 1 in 2,000, 1 in 4,000, 1 in 8,000, 1 in 16,000, and 1 in 32,000.

These dilutions were freshly made from the stock of concentrated serum immediately before performing the tests, as antitoxin in such high dilutions has been shown to lose its potency rapidly.

The diluting fluid was sterile normal saline solution.

As a control I injected intracutaneously, into each of the patients tested, .2 ccm. of 1 in 100 dilution of concentrated Diphtheria antitoxin and in none of the cases did blanching occur in the control tests.

Readings were taken, in all cases, twelve hours after performing the tests and a positive reaction was regarded as one showing an area of definite blanching, measuring $\frac{10}{10}$ mm. or over, around the site of injection.

In all, eighteen patients were tested, their ages varying from 4 - 14 years and each showed a generalised bright punctate erythema of less than forty-eight hours duration.

In nine cases samples of Messrs Parke Davis & Co. serum were used and, in the remaining nine cases, that of Messrs Burroughs Wellcome & Co.

Results obtained:-

1. Positive reaction with dilutions up to 1 in 16,000 in four cases showing a rash of under 24 hours duration.
i.e. Minimum blanching dose of serum
= .2 ccm. of $\frac{1}{16,000}$ dilution = .00001 ccm.
2. Positive reaction with dilutions up to 1 in 8,000 in two cases, having a rash of under 24 hours duration.
i.e. /

i.e. Minimum blanching dose of serum

$$= .2 \text{ ccm. of } \frac{1}{8,000} \text{ dilution} = .00002 \text{ ccm.}$$

3. Positive reaction with dilutions up to 1 in 4,000 in the remaining twelve cases, four of whom had rashes of under 24 hours duration and the others of 24 - 48 hours.

i.e. Minimum blanching dose of serum

$$= .2 \text{ ccm. of } \frac{1}{4,000} \text{ dilution} = .00005 \text{ ccm.}$$

Blanching invariably occurred with higher dilutions in rashes of under 24 hours duration and the less satisfactory results were obtained with the rashes which had been present for 24 - 48 hours.

Much therefore seems to depend upon the securing of an early and suitable type of rash and the lack of uniformity in the above set of tests bears out this point.

The results for the two varieties of serum corresponded very closely.

The negative result obtained in all the control tests points to the specificity of the reaction and, provided a sufficient number of early rashes of the typical punctate erythematous type are available for testing, it forms a useful test for estimating the potency of a Scarlet fever antitoxic serum, besides being a valuable diagnostic test for a rash of doubtful origin.

METHOD 2.

Toxin - antitoxin neutralisation as practised by the Dicks²⁷.

The rationale of this method is to find the smallest amount of antitoxin which will neutralise one skin test dose of a standard Scarlet fever toxin in a strongly Dick positive individual.

Having found this quantity we arrive at an estimate of a unit of antitoxin (which neutralises one hundred skin test doses of toxin) and hence can calculate how many units of antitoxin are contained in a given amount (e.g. 1 ccm.) of the antitoxin.

Theoretically this appears a very exacting way of measuring the strength of Scarlet fever antitoxic serum, but the practical difficulties in carrying out the method detract considerably from its accuracy. The toxin used in the following tests was a standard Scarlet fever toxin supplied by Messrs Burroughs Wellcome & Co.

It was described as type X48 and it was used in 1 in 1,000 dilution.

.1 ccm. of X48 toxin was taken as equal to one skin test dose.

Tests were performed upon children whose ages varied between 6 and 14 years.

A/

A Dick test was first performed upon each child, using .1 ccm. of the above toxin which was injected intracutaneously into the flexor aspect of left forearm.

A control test was done upon the right forearm in each case with the same type and dilution of toxin which had been rendered inactive by heat.

This is necessary to eliminate 'pseudo' reactions due to sensitisation to foreign protein.

Readings were taken, in all cases, 24 hours after performing the tests and then only those children showing a strongly positive Dick test ($\frac{10}{10}$ mm. and over), with a negative control, were used for subsequent testing.

With all aseptic precautions I mixed, in separate sterile bottles, equal quantities of 1 in 1,000 dilution of toxin and antitoxin in varying dilutions.

The dilutions of antitoxic serum were as follows:- 1 in 1,000, 1 in 2,000, 1 in 3,000, 1 in 4,000 and 1 in 5,000 - these being freshly made with sterile normal saline solution before use.

The bottles containing these mixtures of toxin and antitoxin were incubated at 37.5°C . for 12 hours to ensure thorough interaction between toxin and antitoxin.

The antitoxic serum used in these mixtures was taken from the stock, being used therapeutically in the/

the Scarlet fever patients.

I was able to obtain sixteen children showing the required positive Dick test and negative control.

Each case received ten intracutaneous injections of .2 ccm. of the above mixtures of toxin - antitoxin, five injections containing mixtures of X48 toxin and Parke Davis antitoxin, and the remaining five containing the same type of toxin and Burroughs Wellcome antitoxin.

In contrasting the two varieties of antitoxic serum it is necessary to apply both to the same patient as individuals vary widely in their susceptibility to these tests.

A further control test was made in each case by the intracutaneous injection of .2 ccm. of 1 in 100 dilution of the antitoxic serum. This was negative (24 hours reading) in all cases showing that patients in question were not sensitive to horse serum.

Readings were taken 24 and 48 hours subsequent to administering the injections.

Complete neutralisation of toxin by antitoxin was shown by a negative result and any reaction showing an area of $\frac{10}{10}$ mm. or over was regarded as positive.

A reading taken 48 hours, as well as 24 hours, after injection is essential owing to the fact that the weaker dilutions of antitoxin will hold the toxin in/

in combination for 24 hours, but later release it, so that a test which is negative 24 hours later may become positive in 48 hours.

Results obtained:-

1. Complete neutralisation occurred in four cases with all mixtures, including that containing one skin test dose of toxin (.1 ccm. of 1 in 1,000 dilution of X48 toxin) and .1 ccm. of 1 in 5,000 dilution of antitoxin, in 24 hours readings but returning positive in 48 hours.

From the above results the calculation of the number of units per ccm. of antitoxin is as follows:-

Amount of antitoxin injected = .1 ccm. $\frac{1}{5000}$ dilution
 i.e. .1 ccm. $\frac{1}{5000}$ solution of Antitoxin = 1 skin test dose of toxin.

∴ 1 ccm. of concentrated antitoxin

= 50,000 skin test doses of toxin

i.e. 500 units of antitoxin are contained in 1 ccm. of the concentrated serum.

N.B. According to these tests potency of serum may exceed the above figure, but higher dilutions of antitoxin were not employed.

2. In four cases the serum was found to neutralise 40,000 skin test doses of toxin per ccm.
3. In three cases it was calculated to equalise 30,000 skin test doses of toxin per ccm. and in one case 20,000 skin test doses.

4. In four cases no neutralisation occurred, the lowest dilution of serum used being 1 in 1,000.

Results by this method vary widely and renders it difficult to draw definite conclusions as to its efficacy.

In only 25% of the tests is the serum found to be of the required strength - namely that 1 ccm. will neutralise 50,000 skin test doses of toxin.

There appears to be a wide margin of error in this method according to the variations in susceptibility of the individuals tested, which would account for the widely divergent results.

In addition to this variation in individual susceptibility the other difficulties of the method are the determination of the exact amount of toxin to constitute a skin test dose, the scarcity of suitable volunteers and the large number of injections necessary in each person.

METHOD 3.

The production of Passive Immunity.

In this method one sets out to find the smallest amount of serum which will render all Dick positive reactors negative and keep them so for a period of time beyond the longest incubation period of Scarlet fever.

This/

This dose of serum should constitute an efficient prophylactic dose of antitoxin and, working on the hypothesis of the Dicks²⁸ that:-

"A prophylactic dose should be one half of a therapeutic dose." we arrive at an estimate of what should form a therapeutic dose of that serum.

The following is a brief description of the method employed:-

The subjects tested were children between the ages of 1 - 12 years.

A Dick test together with a control test (using inactivated toxin) was performed on each child and readings taken 24 hours later.

To those showing a positive Dick test of $\frac{10}{10}$ mm. and over an injection of concentrated Scarlet fever streptococcus antitoxin was given intramuscularly into the lateral aspect of the thigh.

The serum used was again of the same type as that employed therapeutically.

Each individual who received an injection of serum had a Dick test performed 24 and 48 hours after the administration of serum and again on the fifth, seventh and tenth days following such an injection.

A control test was done at the same time in each case to exclude hypersensitiveness to the foreign protein being regarded as a positive reaction.

For the Dick tests I used .2 cc. of 1 in 1,000 dilution/

TABLE 1.

No.	Age	Dick Test.	24 hrs.	48 hrs.	5th day	7th day	10th day.
1.	3 yrs	$\frac{15}{25}$ mm.	neg.	neg.	neg.	$\frac{10}{10}$ mm.	-
2.	6 "	$\frac{15}{20}$ mm.	neg.	neg.	$\frac{10}{10}$ mm.	-	-
3.	10 "	$\frac{30}{20}$	$\frac{18}{30}$ mm.	$\frac{18}{23}$ mm.	-	-	-
4.	10 "	$\frac{10}{15}$	$\frac{15}{12}$	$\frac{15}{15}$	-	-	-
5.	$4\frac{1}{2}$ "	$\frac{15}{20}$	neg.	neg.	neg.	neg.	neg.
6.	9 "	$\frac{30}{20}$	$\frac{10}{12}$	$\frac{10}{20}$	-	-	-
7.	6 "	$\frac{10}{12}$	neg.	neg.	neg.	neg.	$\frac{10}{12}$ mm.
8.	2 "	$\frac{23}{18}$	neg.	neg.	$\frac{10}{15}$	-	-
9.	$4\frac{1}{2}$ "	$\frac{20}{25}$	$\frac{12}{12}$	$\frac{10}{10}$	-	-	-
10.	4 "	$\frac{20}{25}$	$\frac{12}{20}$	$\frac{15}{25}$	-	-	-
11.	4 "	$\frac{25}{20}$	$\frac{10}{15}$	neg.	neg.	$\frac{10}{12}$	-
12.	$2\frac{1}{2}$ "	$\frac{15}{20}$	neg.	neg.	neg.	neg.	neg.
13.	3 "	$\frac{15}{20}$	neg.	neg.	$\frac{12}{20}$	-	-
14.	6 "	$\frac{20}{15}$	neg.	neg.	neg.	neg.	neg.
15.	4 "	$\frac{25}{15}$	neg.	neg.	neg.	neg.	$\frac{12}{15}$
16.	1 "	$\frac{20}{20}$	neg.	neg.	neg.	neg.	$\frac{12}{20}$
17.	2 "	$\frac{25}{20}$	$\frac{10}{15}$	$\frac{10}{10}$	-	-	-
18.	5 "	$\frac{25}{35}$	$\frac{20}{30}$	$\frac{15}{25}$	-	-	-
19.	6 "	$\frac{30}{50}$	$\frac{15}{25}$	$\frac{15}{15}$	-	-	-
20.	6 "	$\frac{10}{10}$	$\frac{10}{10}$	$\frac{10}{10}$	-	-	-

"neg." = negative result to Dick test.

dilution of Messrs Burroughs Wellcome & Co. standard Scarlet fever toxin, type X48, and, for the control test, the same type of toxin rendered inactive by heat.

In my first series of twenty cases each child received an intramuscular injection of $2\frac{1}{2}$ ccm. of Messrs Burroughs Wellcome & Co. concentrated Scarlet fever streptococcus antitoxin.

If the Dick test still remained positive 48 hours after the injection of serum it was considered unnecessary to reapply the test at subsequent intervals, as that dose had been insufficient for prophylactic purposes in terms of the Dick test.

The following table shows the age of child, the initial Dick test and the behaviour of that test subsequent to the injection of serum. (Table 1 - see opposite).

As seen from the figures in Table 1 only 15% of the children remained Dick negative for a period of ten days following the administration of serum, although 50% showed a negative reaction 24 hours after the injection.

From these results it is evident that $2\frac{1}{2}$ ccm. of the serum in question does not form an adequate prophylactic dose in terms of rendering Dick positive reactors negative and keeping them so for a period of ten days.

In/

In my next set of cases, using 3 ccm. of the same type of serum and the same toxin for the Dick test and controls, my results were similar.

TABLE 2.

No.	Age	Dick Test	24 hrs.	48 hrs.	5th day	7th day	10th day
1.	7 yrs	$\frac{20}{35}$ mm.	$\frac{15}{20}$ mm.	$\frac{15}{15}$ mm.	-	-	-
2.	6 "	$\frac{20}{25}$	$\frac{15}{20}$	$\frac{12}{20}$	-	-	-
3.	4 "	$\frac{20}{30}$	$\frac{12}{18}$	$\frac{10}{15}$	-	-	-
4.	6 "	$\frac{20}{25}$	neg.	neg.	$\frac{15}{20}$ mm.	-	-
5.	3 "	$\frac{20}{30}$	$\frac{15}{20}$	$\frac{10}{15}$	-	-	-
6.	$2\frac{1}{2}$ "	$\frac{20}{25}$	$\frac{12}{15}$	$\frac{10}{10}$	-	-	-
7.	5 "	$\frac{20}{25}$	$\frac{13}{25}$	$\frac{15}{25}$	-	-	-
8.	$4\frac{1}{2}$ "	$\frac{20}{25}$	$\frac{18}{20}$	$\frac{15}{15}$	-	-	-
9.	6 "	$\frac{10}{10}$	neg.	neg.	neg.	neg.	neg.
10	$7\frac{1}{2}$ "	$\frac{10}{20}$	neg.	neg.	neg.	neg.	neg.
11	2 "	$\frac{20}{25}$	neg.	neg.	neg.	$\frac{10}{15}$ mm.	-

"neg" = negative result to Dick test.

Only 18% of these children remained Dick negative for 10 days following the intramuscular injection of 3 ccm. of the antitoxin.

I next employed a dose of 5 ccm. and tested this upon a series of twenty-five Dick positive children.

TABLE 3.

No.	Age	Dick Test.	24 hrs.	48 hrs.	5th day.	7th day.	10th day.
1.	2 yrs	$\frac{20}{25}$ mm.	$\frac{10}{10}$ mm.	neg.	$\frac{25}{25}$ mm.	-	-
2.	5 $\frac{1}{2}$ "	$\frac{25}{20}$	$\frac{12}{15}$	$\frac{25}{20}$ mm.	-	-	-
3.	4 $\frac{1}{2}$ "	$\frac{20}{33}$	$\frac{15}{20}$	$\frac{20}{30}$	-	-	-
4.	8 "	$\frac{15}{25}$	$\frac{30}{20}$	$\frac{15}{10}$	-	-	-
5.	3 "	$\frac{20}{20}$	neg.	neg.	neg.	neg.	neg.
6.	3 "	$\frac{12}{10}$	neg.	neg.	neg.	neg.	neg.
7.	4 "	$\frac{40}{30}$	$\frac{20}{30}$	$\frac{15}{15}$	-	-	-
8.	2 "	$\frac{30}{20}$	$\frac{10}{15}$	neg.	neg.	neg.	neg.
9.	4 $\frac{1}{2}$ "	$\frac{15}{20}$	neg.	neg.	neg.	neg.	neg.
10.	2 "	$\frac{23}{18}$	neg.	neg.	neg.	neg.	neg.
11.	4 "	$\frac{25}{20}$	$\frac{15}{20}$	$\frac{10}{10}$	-	-	-
12.	2 "	$\frac{20}{15}$	$\frac{15}{20}$	neg.	neg.	neg.	neg.
13.	4 "	$\frac{25}{35}$	$\frac{20}{30}$	$\frac{20}{20}$	-	-	-
14.	6 "	$\frac{20}{30}$	$\frac{15}{15}$	neg.	neg.	neg.	neg.
15.	5 "	$\frac{25}{30}$	neg.	neg.	neg.	$\frac{10}{12}$ mm.	-
16.	4 "	$\frac{15}{25}$	$\frac{15}{25}$	neg.	$\frac{10}{10}$	-	-
17.	3 "	$\frac{15}{15}$	neg.	neg.	neg.	neg.	neg.
18.	6 "	$\frac{30}{25}$	$\frac{13}{15}$	$\frac{10}{10}$	-	-	-
19.	1 "	$\frac{25}{25}$	$\frac{15}{20}$	$\frac{10}{15}$	-	-	-
20.	4 "	$\frac{30}{35}$	neg.	neg.	neg.	neg.	neg.
21.	5 "	$\frac{20}{15}$	neg.	neg.	neg.	neg.	neg.
22.	4 $\frac{1}{2}$ "	$\frac{12}{20}$	neg.	neg.	neg.	neg.	neg.
23.	2 "	$\frac{12}{20}$	neg.	neg.	neg.	neg.	neg.
24.	4 "	$\frac{20}{20}$	neg.	neg.	neg.	neg.	neg.
25.	4 "	$\frac{12}{18}$	neg.	neg.	neg.	neg.	neg.

"neg" = negative result to Dick test.

The above table shows that 56% of the children who had received an intramuscular injection of 5 ccm. of the serum remained Dick negative for ten days following the injection.

Unfortunately during these experiments the supply of X48 toxin became exhausted and was unable to be replaced.

I was supplied, by Messrs Burroughs Wellcome & Co., with a standard Scarlet fever toxin type B.3015.

It was used in 1 in 1,000 dilution and the usual amount of .2 ccm. was used for testing.

The control test was performed with this same type of toxin rendered inactive by heat.

This toxin appeared to be much less potent than the X48 type and gave a much smaller percentage of positive reactors amongst the children tested.

Using the X48 toxin I was getting, in children who did not give a history of Scarlet fever, over 90% of positive reactors; while with the B.3015 type of toxin the number of positives dropped to about 50 - 60%.

Hence the results in this table are difficult to interpret for in the case of the last six children in the above table, in whom I used type B.3015 toxin for the Dick tests, all gave a negative reaction in 24 hours and remained so for ten days.

A further series of twenty cases, in whom I used/

TABLE 4.

No.	Age.	Dick Test.	24 hrs.	48 hrs.	5th day.	7th day.	10th day.
1.	6 yrs	$\frac{22}{40}$ mm.	$\frac{12}{15}$ mm.	neg.	neg.	neg.	neg.
2.	6 "	$\frac{15}{20}$	$\frac{15}{20}$	neg.	neg.	neg.	neg.
3.	3 "	$\frac{10}{20}$	neg.	neg.	neg.	neg.	neg.
4.	3 "	$\frac{20}{20}$	neg.	neg.	neg.	neg.	neg.
5.	7 "	$\frac{15}{25}$	neg.	neg.	neg.	neg.	neg.
6.	4 "	$\frac{15}{25}$	neg.	neg.	neg.	neg.	neg.
7.	5 "	$\frac{15}{25}$	neg.	neg.	neg.	neg.	neg.
8.	2 "	$\frac{20}{20}$	neg.	neg.	neg.	neg.	neg.
9.	4 "	$\frac{20}{25}$	$\frac{10}{15}$	neg.	neg.	neg.	neg.
10.	4 "	$\frac{20}{18}$	neg.	neg.	neg.	neg.	neg.
11.	5 "	$\frac{15}{25}$	$\frac{12}{15}$	$\frac{10}{15}$ mm.	-	-	-
12.	5 "	$\frac{22}{30}$	neg.	neg.	neg.	neg.	neg.
13.	4 "	$\frac{15}{20}$	neg.	neg.	neg.	neg.	neg.
14.	10 "	$\frac{20}{25}$	neg.	neg.	neg.	neg.	neg.
15.	5 "	$\frac{25}{35}$	$\frac{10}{15}$	neg.	neg.	neg.	neg.
16.	7 "	$\frac{25}{40}$	$\frac{12}{12}$	neg.	neg.	neg.	neg.
17.	5 "	$\frac{20}{20}$	neg.	neg.	neg.	neg.	neg.
18.	6 "	$\frac{15}{25}$	neg.	neg.	neg.	neg.	neg.
19.	2 $\frac{1}{2}$ "	$\frac{16}{18}$	neg.	neg.	neg.	neg.	neg.
20.	7 "	$\frac{15}{18}$	neg.	neg.	neg.	neg.	neg.

"neg." = negative result to Dick test.

used B.3015 toxin for the Dick tests and who received an intramuscular injection of 5 ccm. of Messrs Parke Davis & Co. concentrated Scarlet fever streptococcus antitoxic serum, gave results as shown in the following table:- (Table 4 - see opposite).

In table 4 we see that 95% of the children tested became Dick negative within 48 hours and remained so for ten days following the intramuscular administration of 5 ccm. of the serum in question.

From these data it may be concluded that, with regard to the sera used, a minimum of 5 ccm. should be given for an efficient prophylactic dose and, from that, one might deduce that, for therapeutic purposes, a dose of 10 ccm. of these sera should be recommended.

The potency of the X48 type of toxin as compared with the B.3015 renders the test of the efficacy of the serum, in the earlier series of cases, a severe one and leaves it open to doubt as to what the results would have been, using a smaller quantity than 5 ccm. of the serum together with type B.3015 toxin for applying the Dick tests.

Thus the chief practical difficulty in this method is the securing of a reliable standard toxin for the purposes of the Dick test.

DOSAGE OF SERUM.

On this vital question the opinions of different authorities have varied.

In the early days of antitoxin therapy, with regard to Scarlet fever, the methods of standardisation and concentration were not in vogue and hence the dosage of these sera was an uncertain quantity and differed widely in the hands of their users.

Many of the unsatisfactory results were thus probably due to insufficient dosage and to sera of feeble potency appearing on the market through lack of any reliable method of testing their strength.

The Dicks²⁷ at first considered a therapeutic dose to be one which neutralised 20,000 skin test doses of toxin.

Blake and Trask²¹ were of the opinion that a dose able to neutralise between 200,000 - 1,000,000 skin test doses of toxin was necessary, according to the severity of disease.

Other observers including Anderson and Leonard³¹ and Gordon³⁴, agreed that, for the average case of Scarlet fever, a therapeutic dose was an amount equivalent to 200,000 skin test doses of toxin.

Thus one may take as a general rule that an amount of serum able to neutralise between 200,000 - 1,000,000 skin test doses of a Standard Scarlet fever toxin/

toxin to be sufficient, as far as our knowledge goes, for the average case of Scarlet fever.

To each of the patients in the series of three hundred and sixty-five cases of Simple Scarlet fever I gave the recommended dose of 10 ccm. which was supposed to neutralise 500,000 skin test doses of toxin.

Two hundred and seven cases received the serum of Messrs Parke Davis & Co., while the remaining one hundred and fifty-eight were given that of Messrs Burroughs Wellcome & Co.

The method of administration in every case was by intramuscular injection into the lateral aspect of the thigh.

The nine cases of Septic Scarlet fever were treated by an intramuscular injection of 10 ccm. of the Concentrated Scarlet fever streptococcus antitoxin followed by 50 ccm. of Polyvalent Antistreptococcal serum (Messrs Burroughs Wellcome & Co.)

To the two cases of toxic Scarlet fever the therapeutic dose of 10 ccm. was repeated 12 hours later in both cases.

TABLE 5.

Age Period in years.	Admission to Hospital and Day of disease on which Serum was administered.											
	First		Second		Third		Fourth		Totals.			
	S.	C.	S.	C.	S.	C.	S.	C.	S.	S.	C.	
0 - 5 yrs.	19.	10.	43.	47.	29.	31.	3.	3.	94.	101.		
5 - 10 "	12.	12.	90.	84.	50.	47.	2.	2.	154.	145.		
10 - 15 "	6.	5.	15.	17.	26.	26.	5.	7.	52.	55.		
15 & over	3.	3.	21.	21.	30.	31.	11.	9.	65.	64.		
Totals	40.	40.	169.	169.	135.	135.	21.	21.	365.	365.		

S = serum treated case.

C = control case.

RESULTS OF SERUM TREATMENT.

I propose to summarise separately the results of serum treatment in the three types of the disease under consideration, viz. Simple, Septic and Toxic Scarlet fever.

SIMPLE SCARLET FEVER.

This series consists of three hundred and sixty-five cases treated with concentrated Scarlet fever streptococcus antitoxic serum during the first four days of disease, together with a similar number of control cases treated on purely symptomatic lines.

The following table shows the age groups of the serum treated, and control cases, and the day of disease on which the patients were admitted to Hospital.

All patients having serum treatment received the injection on the day of admission to Hospital. (Table 5 - see opposite).

In evaluating the effects of antitoxic serum I wish to draw particular attention to the following salient points in the clinical course of the disease.

1. Temperature Curve.
2. Nervous manifestations.
3. Duration of Rash and degree of Desquamation.

4. /

4. Serum Reactions.
5. Incidence of Complications.
6. Duration of stay in Hospital.
7. Incidence of Relapses and Second attacks of the disease.
8. Case Mortality.

Temperature Curve.

The duration of Pyrexia subsequent to admission to hospital is shown in the following table:-

TABLE 6.

Duration of Pyrexia in hours	Admission to Hospital and Day of Disease on which serum was administered.									
	First		Second		Third		Fourth		Totals.	
	S	O.	S	O.	S	O.	S	O.	S	O.
Under 24 hrs	14	9	48	46	43	36	5	9	110	100
24-48 "	21	23	94	72	73	46	11	10	199	151
48-72 "	3	2	15	35	13	39	3	2	34	78
over 72 "	2	6	12	16	6	14	2	0	22	36
Totals	40	40	169	169	135	135	21	21	365	365

S = serum treated case. O = control case.

In cases of simple Scarlet fever the temperature normally falls on the 3rd - 5th days of disease, irrespective of serum treatment, and so reduction of pyrexia, unless very dramatic, is difficult to ascribe to the effects of serum treatment.

A fall of temperature to normal within 24 hours of/

of the injection of serum was noted in one hundred and ten cases.

However, almost identical curves were obtained in no fewer than one hundred control cases.

Forty-eight hours after the injection of serum three hundred and nine patients showed temperatures returned to normal while in the control series two hundred and fifty-one patients showed a similar temperature curve.

Of the serum treated cases the temperatures of twenty-two patients remained above normal for a period exceeding 72 hours and in the control series the number of cases showing pyrexia beyond that period of time after admission to hospital was thirty-six.

In a few of the serum treated cases there was a small rise in temperature 2-4 hours after the injection due to a reaction to the foreign protein.

On the whole, pyrexia is reduced more rapidly in the cases treated with serum.

Coincident with the decline of temperature there is a return of the pulse rate to normal.

Nervous Manifestations.

The toxin of Scarlet fever apparently acts as an exciting factor to the nervous system whereas that of Diphtheria acts as a depressant.

Practically all the cases, to whom serum was administered/

administered on the evening of admission to Hospital, showed marked improvement in the toxaemic manifestations of the disease within 12 hours of the injection.

This is most easily judged in the case of adult patients who invariably admitted that they had been rendered much more comfortable and that they felt relatively well within a short time of receiving the treatment.

Cushing,³² in his observations of five hundred cases treated with serum, aptly remarks that:-

"The whole aspect of acute Scarlet fever wards has been changed since the general use of serum as there are practically no sick patients."

Effects on Rash and Desquamation.

The rash is one of the several manifestations of the effects of the toxin of the causal organism and so it is to be expected that, by the prompt administration of the specific antitoxin (the purpose of which is to neutralise that toxin), the disappearance or blanching of the exanthem before its normal time should occur.

This is best seen in the early rashes of about 24 hours duration in which cases the neutralisation was most strikingly shown by the decided diminution in intensity or complete disappearance in 12-24 hours after/

after the injection of serum.

Out of the total of three hundred and sixty-five cases 60% showed complete blanching of the rash within 24 hours of giving the serum.

In some cases the rash showed little or no blanching beyond normal limits.

This fact may be ascribed to lack of specificity on the part of the antitoxin towards the toxin elaborated by the particular causal strain of haemolytic streptococcus; also to rashes of over 24 hours duration becoming stained into the tissues of the skin and unable to be blanched by the antitoxin.

With regard to desquamation it was found to be the general rule that in those cases which showed complete or modified blanching of the rash within 24 hours there was an absence or almost imperceptible form of desquamation.

Serum Reactions.

In former days the 'bête noir' of all serum therapy was the severe reactions following the administration of the foreign protein and in some cases these were more severe than the actual disease.

It is now generally recognised that, with the modern methods of concentrating the various preparations of serum, the results of this dread occurrence have been very considerably reduced.

Provided/



Provided due care is taken to enquire into any history of an asthmatic or allergic tendency and to desensitise any cases who had previously received an administration of horse serum, there is little likelihood of untoward results following the use of a reliable concentrated antitoxic serum.

In the above series of cases one hundred patients (27%) showed reactions at intervals of 4 - 16 days following the injection.

In no case did the symptoms give rise to alarm.

In seventy-five of these cases a rash was noted, usually urticarial in nature, which lasted for three days in the most severe cases, but was usually only of a few hours duration.

The remaining twenty-five cases showed definite symptoms of the serum disease in the form of slight pyrexia, adenitis, fleeting joint pains and an accompanying urticarial eruption lasting 1 - 3 days.

Calcium chloride has enjoyed a certain reputation in minimising these serum reactions and an attempt was made to obviate these unpleasant phenomena by the administration of this drug given orally in doses of grs. X. thrice daily to adults and grs. V to children.

In all some eighty cases were treated thus for ten days following the injection of serum, but it was found that the drug had no effect in preventing or alleviating these reactions.

The percentage of serum reactions in these cases was similar to those not receiving the calcium therapy.

Incidence of Complications.

The power which a serum possesses to reduce or prevent the various complications associated with Scarlet fever forms one of the main lines of investigation of the clinical benefits of such a therapeutic measure.

The present day type of Scarlet fever in this country shows such a low case mortality that it is difficult to judge the merits of a serum in further reducing this figure and a careful study of its effects upon the dreaded complications, which are responsible for the prolonged hospitalisation of some patients and the incomplete recoveries and infirmities resulting from an attack of the disease, has justified its clinical application as a means of combating the undesirable effects of this particular malady.

All observers are agreed upon the marked improvement which a specific antitoxic serum exerts upon the early toxæmia of the disease, but I think nobody has yet claimed that it altogether prevents the well known complications of Scarlet fever, even when given as early as possible.

On the other hand it is only reasonable to expect that any treatment which is going to shorten the disease and benefit the general condition of the patient (both of which Scarlet fever streptococcus antitoxin/

TABLE 7.

Complications.	Admission to Hospital & day of Disease on which Serum was administered							
	First		Second		Third		Fourth.	
	S	C	S	C	S	C	S	C
Adenitis (late non-suppurative)	5	7	12	23	15	16	2	2
Adenitis (late suppurative)	2	-	1	-	1	1	-	-
Purulent Rhinitis	2	8	6	4	2	5	1	-
Arthritis	-	-	4	3	2	5	2	2
Otitis Media	-	1	7	3	6	10	2	-
Nephritis	-	-	-	-	1	1	1	-
Nephritis, Otitis Media	-	-	-	1	-	-	-	-
Nephritis, Adenitis	-	-	-	1	-	-	-	-
Adenitis, Purulent Rhinitis	1	-	3	8	2	3	-	1
Purulent Rhinitis, Otitis Media	2	3	1	4	1	3	1	-
Adenitis, Arthritis	-	-	-	5	-	2	-	-
Adenitis, Otitis Media.	-	1	3	6	1	1	-	-
Otitis Media, Arthritis	-	-	-	-	-	-	-	1
Otitis Media, Jaundice	-	-	-	-	-	1	-	-
Rhinitis, Otitis Media, Adenitis	-	3	2	3	1	2	-	-
Adenitis, Rhinitis, Lobar Pneumonia	-	-	1	-	-	-	-	-
Lobar Pneumonia, Empyema	-	-	1	-	-	-	-	-
Broncho-Pneumonia	-	-	-	1	-	-	-	-
Pleurisy with Effusion	-	-	-	-	-	1	-	-
Septic Dermatitis	-	-	-	-	-	-	1	-
Totals	12	23	41	62	32	51	10	6

S = serum treated case.

C = control case.

antitoxin has been shown to do) will lessen the number and severity of complications as the resisting powers of the patient are improved.

This point is amply borne out by the statistics of workers upon the subject.

Blake and Trask²¹ are of opinion that, when antitoxin is given as early as possible,

"The probability that subsequent complications will develop is small" and Robb²⁵ as a result of his experiences of one hundred and forty cases treated with serum concludes that we may look for a great reduction in the serious complications and sequelae of Scarlet fever.

A comparison between the incidence of complications in three hundred and sixty-five cases treated with serum and a similar number of non-serum treated cases of Simple Scarlet fever is detailed in the following table. (Table 7 - see opposite).

As shown in table 7, out of a total of three hundred and forty-four cases treated with serum during the first three days of disease, complications developed in eighty-five, while in a similar number of control cases complications were noted in one hundred and thirty-six.

With each day of delay in the administration of the antitoxin the incidence of complications amongst the/

the serum treated cases tends to approximate more closely to that in the control series.

This speaks for the necessity of the early giving of antitoxin as soon as the diagnosis is made, for, as depicted in the above table, out of forty cases treated on the first day of disease only twelve developed complications whereas the control series showed an incidence of twenty-three from a similar number of cases admitted to Hospital on the first day of disease.

The greater number of complications in the serum-treated over those in the control cases amongst patients coming under treatment on the fourth day of disease, though partly explained by the fact that such cases were of a more severe type to whom it was thought advisable to give antitoxin even at this relatively late stage, suggests that by this period the optimum time for serum treatment is past.

Multiple complications occurred in twenty of the serum treated and in forty-nine of the non-serum treated cases.

In the following table the incidence of Arthritis, Nephritis and Otitis Media in three hundred and forty-four cases who received serum during the first three days of disease is contrasted with that in a corresponding number of control cases.

TABLE 8./

TABLE 8.

Complications	S.	C.
Arthritis	6.	15.
Nephritis	1.	3.
Otitis Media	24.	42.

S = serum treated case. C = control case.

The cases of Arthritis occurred almost exclusively amongst adult female patients.

In one such case the temperature continued to swing from 5th - 12th days of disease and the joints affected were those of the upper extremities.

Cases were sub-acute in type with no obvious swelling or redness of the affected joints, the chief complaints being pain and stiffness.

The possibility of the joint condition being due to a serum phenomenon was carefully excluded and none of the above six cases showed any other signs or symptoms of a serum reaction.

The case of Nephritis in the serum-treated cases occurred in a female patient aged 12 years who received her injection on the third day of disease.

Temperature and pulse reached normal 36 hours after the injection and the clinical course was uneventful till the eighteenth day, when the temperature/

temperature shot up to 101⁰F. and remained high for 48 hours when it again returned to normal.

Only a trace of albumen, too small to be registered quantitatively, was present from 19th - 21st days of disease.

The amount of urine passed on these days was twenty-three and thirty ozs. respectively.

On the nineteenth day of disease a few granular casts were seen on microscopic examination, but repeated examinations of specimens on subsequent days failed to show the presence of casts.

There were no clinical symptoms of nephritis such as gastro-intestinal disturbances and there was no oedema.

The case was thus one of a mild abortive type and the patient made a perfect recovery.

The frequency of Otitis Media in the serum-treated cases was only slightly over 50% of that in the control series. The otitis media was complicated by mastoiditis, necessitating operation, in one of the serum-treated and in two of the control cases.

Duration of Stay in Hospital.

The general procedure in the Edinburgh City Fever Hospital is that uncomplicated cases of Scarlet fever are discharged from the wards on the 28th day of disease and, after receiving their disinfecting bath, /

bath, are detained in a convalescent ward for two or three days before returning home.

All complicated cases and those showing the slightest signs of any infective discharges are detained until free from such.

This routine has not been altered in the case of serum-treated patients, all of whom were kept in Hospital for the usual twenty-eight days in the absence of any complications and, in the event of such happenings occurring, until these were entirely cleared up and beyond all risk of infection to others.

It has been suggested by various observers among whom Robb,²⁵ from his experiences of serum therapy in Scarlet fever, is of the opinion that:-

"By cutting down the necessary quarantine period we may hope for much relief to the strain which Scarlet fever puts on the accommodation in Fever Hospitals."

Investigations carried out by Gordon³⁴ showed that haemolytic streptococci disappeared from the nose and throat sooner in serum-treated than in non-serum-treated cases.

Cultures were taken when patients were admitted to Hospital, when all cases yielded haemolytic streptococci.

Cultures were repeated on the 7th, 14th and 28th days of disease.

The /

The difficulties in the identification of these organisms and the technique required to prove them to be the specific strains of haemolytic streptococcus associated with Scarlet fever renders this method of terminating the quarantine of Scarlet fever impracticable at present.

This point is important from the Public Health aspect in relation to the return case-rate, but it is not yet feasible to adopt it as a routine method of determining quarantine as in Diphtheria.

With regard to the question of serum therapy shortening the quarantine period Cushing³² assumes that this is not so except that, by lessening the number of septic complications, the average quarantine will be shortened.

Thus, not only by lessening the number of complications but also by diminishing their severity and duration, antitoxin plays an important economic part in lessening the congestion in Scarlet fever wards caused by the prolonged period of isolation of patients suffering from the various septic complications associated with the disease.

In my series of three hundred and sixty-five cases treated with serum the total number of days in Hospital beyond the usual twenty-eight was 2035 which, when contrasted with the figure 3015 for the same number of control cases, speaks favourably for serum/

serum treatment in lessening the necessary period of hospitalisation.

Incidence of Relapses.

This question naturally presents itself in the antitoxin treatment of any disease whereby the specific toxin of the infecting organisms is neutralised by the corresponding antitoxin and the natural stimulus to the patient's tissues actively forming their own antibodies is lost.

Thus, what may be termed a non-sterilising immunity is set up which increases the liability to relapses and subsequent attacks.

A relapse is regarded as a recurrence of the fever with all the typical clinical symptoms of the primary disease before complete recovery from the initial attack.

This usually occurs during the 3rd - 5th weeks of the disease.

The general incidence of such an occurrence is stated by various authorities to be about 1%.

Amongst the three hundred and sixty-five cases treated with serum there were three genuine relapses occurring during the fourth week of the disease, thus giving a percentage of .8 which cannot be regarded as exceeding normal limits.

Case Mortality.

As previously stated the case-mortality from Scarlet fever at the present time is very low and has been steadily diminishing for the past number of years.

For the year 1926 the rate for the City Fever Hospital Edinburgh was 1.99% and Goodall³⁶ informs us that in London the case-mortality rate has not been above 2% since 1910.

Cushing³² gives us the following data regarding the influence of serum treatment upon the mortality from the disease:-

"At Alexandra Hospital, Montreal, in 1923 the case mortality was 3.25% and since the general use of serum that mortality has fallen to 1.2%; of these none died directly from Scarlet fever but from some concurrent disease."

He says:- "I have yet to see a straight case of Scarlet fever which has received an average dose of serum within the first three days die of the disease."

Only one death occurred among the three hundred and sixty-five cases of Simple Scarlet fever treated with serum.

This was in the case of a female infant aged 1 year who received serum on the first day of disease.

Adenitis developed on the 14th day and suppuration/

suppuration ensued on the 24th day requiring an incision to be made.

Temperature kept normal and progress was fairly satisfactory till the 5th week of disease when temperature reached 100°F and kept swinging for fourteen days, attaining a maximum of 104°F.

Abdomen became greatly distended and free fluid was present in the peritoneal cavity. Child died at end of 9th week of disease. Nothing abnormal was detected in the lungs and a tentative diagnosis of Peritonitis, pneumococcal or tubercular in origin, was made.

A post-mortem examination was not granted.

In the control series there was also one death.

It was that of a child aged 7 years, admitted to Hospital on the 1st day of disease and who later developed a combination of Adenitis, Rhinitis and Otitis Media and died from a septic type of the disease on the thirteenth day after admission to Hospital.

SEPTIC SCARLET FEVER.

This type of the disease is responsible for the majority of severe and fatal cases.

It is characterised by an exaggeration of all the/

the usual symptoms of Simple Scarlet fever together with intense faucial inflammation and a tendency to the development of septicaemic manifestations.

Regarding the etiology of the condition there is, in addition to the toxæmia resulting from infection with the specific strains of the haemolytic streptococcus of Scarlet fever, an invasion of the system by these organisms together with the usual pyogenic organisms found in the naso-pharyngeal flora.

Thus the tissues already weakened by the specific toxæmia of Scarlet fever are rendered more vulnerable to the onslaught of these secondary organisms which are the chief causal agencies in the production of the various septic elements (purulent rhinitis, adenitis, otitis media, septicaemia, etc.) associated with this type of the disease.

It is in this variety of the disease that the most conflicting results of serum therapy have been obtained.

By the administration of Scarlet fever streptococcus antitoxin to definite cases of Septic Scarlet fever it seems to be the general opinion that the septic manifestations of the disease fail to be influenced directly by such a serum.

However, provided the toxæmic element of the disease is still present, as evidenced by the rash etc., it is to be expected that serum therapy will prove/

prove beneficial for, by relieving the patient of the toxaemia, it places that patient in a more fit condition to combat the septic phase of the malady.

Once the specific toxaemia of Scarlet fever is past there is little likelihood of any material benefit resulting from the administration of Scarlet fever streptococcus antitoxin.

Thus, though a critical cure in such cases was not anticipated following the giving of such an antitoxic serum, I was guided by the results of previous observers, among whom Blake and Trask²¹ are of the opinion that:-

"In cases in which septic complications are present on admission to Hospital, antitoxin should likewise be given at once, provided the rash is still present.

The specific toxaemia will be rapidly cured and the septic processes thus favourably influenced."

The serum which I used therapeutically, being prepared from horses by the injection of live virulent cultures of the organisms as well as their toxins, may be claimed to possess antibacterial as well as antitoxic properties and hence it is assumed that these preparations will be more advantageous than a purely antitoxic serum in septic cases where, in addition to the specific toxaemia of the disease there is actual invasion of the tissues by the infecting/

infecting organisms.

The treatment of septic Scarlet fever by a polyvalent antistreptococcal serum, though it has not met with success in all hands, has nevertheless had encouraging results with some observers including Compston¹³ and Goodall¹² who believed that 50 ccm. of a polyvalent antistreptococcal serum injected early in septic cases produced marked improvement.

So, by the combined administration of the two types of serum:-

1. Scarlet fever streptococcus antitoxic serum.
2. Polyvalent antistreptococcal serum.

it was hoped to bring about improvement simultaneously in the two aspects of the infection, viz:- the specific haemolytic streptococcus of Scarlet fever and the secondary pyogenic organisms.

During the period Oct. 1926 - April 1927, I had the opportunity of treating nine cases of Septic Scarlet fever with this dual serum therapy.

The series being extremely limited it is therefore impossible to draw any definite conclusions, but the opinion formed of its efficacy is favourable.

The dose of Scarlet fever streptococcus anti-toxin was 10 ccm. given intramuscularly. Six of the patients received the concentrated preparation of Messrs Parke Davis & Co. and the remaining three that of Messrs Burroughs Wellcome & Co.

The /

The polyvalent antistreptococcal serum was prepared by Messrs Burroughs Wellcome & Co. and given in doses of 50 ccm. intramuscularly.

In one case, owing to the severity of the symptoms this dose was repeated 24 hours later.

As was to be expected from these large doses of foreign protein the serum reactions occurred in five out of the nine cases treated.

They were fairly sharp in nature, but in no case gave rise to any anxiety or untoward results.

The cases were all of a very severe type with temperature of 101-103°F on admission and marked exaggeration of the faucial condition.

Purulent Rhinitis and Cervical Adenitis were present on admission in almost all the cases.

Apart from the serum therapy the only treatment applied to these cases was the usual antiseptic lavage of the mouth and frequent irrigation of the fauces with normal saline.

Six of the above cases, after a febrile period varying from 1-12 days after the injections of serum, experienced an uninterrupted convalescence with no further complications and were discharged from Hospital during the fifth week of disease, i.e. only a few days beyond the normal quarantine period of twenty-eight days.

Two cases developed Otitis Media on the 7th and 12th/

12th days respectively, necessitating a stay in Hospital of nine weeks in both cases.

The remaining case had Bronchitis towards the end of the first week of disease and this condition later developed into Broncho-Pneumonia during the fifth week of disease. Child was discharged from Hospital at the end of the 9th week of disease.

There were no deaths amongst the above cases.

TOXIC SCARLET FEVER.

This type of the disease, which is fortunately the least common, is characterised by a toxæmia out of all proportion to the degree of inflammatory reaction in the throat.

The rash is ill developed, nervous symptoms are prominent and there is uncontrollable diarrhoea and vomiting leading usually to a rapidly fatal issue.

The patient from the first is overwhelmed by the degree of toxæmia and his tissues fail to react so that the usual signs and symptoms of the disease are poorly developed.

It is in this type of the disease that we look for the most dramatic results from specific serum therapy, if given in sufficient dosage and early enough in the course of the disease before the patient is beyond the power to respond to its effects.

The /

The following two cases, which may be regarded as genuine examples of Toxic Scarlet fever, were admitted to the City Fever Hospital, Edinburgh, during the period October 1926 - April 1927.

They were treated with specific antitoxic serum and I propose to give a brief résumé of the clinical course in each case.

CASE 1.

Female aged 7 years.

Case of Scarlet fever from same household in Hospital and two more cases admitted on same day.

Admitted to Hospital on second day of disease.

Condition on Admission.

Temperature 103.8°F. Pulse 168. ? Respirations 36.
Pulse soft and thready. Rash poorly developed.
Lips cyanosed. Tongue furred and dry. Fauces congested. Severe vomiting and diarrhoea. Inability to retain anything by mouth or rectum. Very restless
Semi-delirious.

10 ccm. of Parke Davis concentrated Scarlet fever Streptococcus antitoxin given intramuscularly on admission.

Progress Notes.

Very little improvement in general condition
12 hours later.

16 hours after the first injection of serum:-
10 cc. of the same type of serum given intravenously
in $\frac{1}{2}$ pint of sterile normal saline.

Very marked improvement within 12 hours of the
second injection.

Vomiting and diarrhoea ceased.

Restlessness gone and patient had a comfortable night.
Temperature and pulse reached normal 24 hours after
the second injection, and remained so throughout.
There was no serum reaction.

There were no complications and convalescence,
after the day following the second injection of serum,
was uneventful.

Patient was discharged from Hospital on the 37th
day of disease.

CASE 2.

Female aged 10 years.

Admitted to Hospital on third day of disease.

Condition on Admission.

Temperature 103°F . Pulse 156. Respirations 32.

Ill-developed punctate erythema over trunk.

Tongue and fauces - typical. Slight cyanosis.

Pulse rapid and soft. Extreme restlessness. Marked
diarrhoea. No vomiting.

10 ccm. of Burroughs Wellcome concentrated Scarlet
fever/

fever streptococcus antitoxin given intramuscularly on admission.

Progress notes.

No definite improvement in general condition 12 hours later.

12 hours after first injection of serum -

Attempt to give serum intravenously failed so 10 ccm. of the same type of serum were given intramuscularly. Decided improvement within 24 hours of second injection. Restlessness and diarrhoea ceased. Temperature and pulse reached normal within 48 hours and rash was blanched within 24 hours.

There was no serum reaction.

Convalescence was uninterrupted and patient was discharged from Hospital on 34th day of disease.

The above two cases would almost certainly have had a fatal termination in the absence of serum therapy and the striking improvement produced within 24 hours, establishing convalescence from that time onwards, leaves little doubt that the prompt administration of a sufficient dose of a reliable concentrated Scarlet fever streptococcus antitoxin is a potent antidote for this type of the disease which was previously regarded as almost invariably fatal.

DISCUSSION ON RESULTS OBTAINED.

In the investigation of any therapeutic measure with regard to Scarlet fever it is essential to have at your disposal sufficient clinical material and a reliable method of controlling your results before you base your conclusions.

As previously stated, with the gradual lessening of severity in the type of disease prevalent at the present time, a biased mind will easily be misled by the apparent efficacy of any so-called remedy, unless one is alive to the fact that, up to a certain point, equally satisfactory results would probably have been obtained with purely conservative treatment.

The light which recent investigations have thrown upon the etiology of Scarlet fever has so completely revolutionised its treatment and methods of control that we are now able to attack the disease from standpoints unable to be appreciated by previous observers.

Yet, new as these discoveries seem, the etiological relationship of certain strains of streptococci to Scarlet fever was first conceived by workers as far back as 1886 and towards the end of the nineteenth century antistreptococcal serum was used in the treatment of the disease.

Owing/

Owing to lack of bacteriological knowledge and efficient methods of production and standardisation, serum therapy, with regard to Scarlet fever, enjoyed intermittent phases of favour and misfortune for some considerable time.

I have endeavoured, as far as possible, in my survey of the literature upon the subject to give a comprehensive study of the results of the various workers in this branch of medical science and it is now my purpose to give an account of the points of similarity and any differences which may exist between my own findings and those previously recorded.

The stress laid upon the necessity of taking into account a long series of cases is obvious, for, in statistics from any source, the fallacy of small numbers is one of the chief pit-falls and it may be generally stated that the smaller the number of cases observed the less reliable are the results.

This point is frequently brought forward by previous workers who, through lack of sufficient supplies of serum or due to scarcity of clinical cases, were unable to treat a sufficiently large number of cases for their observations to be conclusive.

In this respect my series of three hundred and sixty-five cases compares favourably with that of other workers and as far as I am aware, with the exception of Cushing³² who treated five hundred cases, it/

it forms the largest number yet recorded.

The question of securing adequate control cases treated on conservative lines is of prime importance in evaluating any therapeutic measure in Scarlet fever.

The Dicks²⁷ amongst others emphasised this fact and most observers have been careful to control their results, though there are some notable exceptions to this rule.

The method of choice in selecting control cases is to study a similar number of cases occurring in the same district, at the same period of time and being comparable in all respects clinically to those cases treated with serum.

Since I was unable to procure an adequate number of suitable control cases occurring at the same period of time as the cases treated with serum, I was obliged to choose the only alternative of selecting cases which occurred during the corresponding period of the previous year.

These cases were chosen from the Edinburgh City Fever Hospital records and, as mentioned previously, were comparable in all details to the cases treated with serum, and thus furnished a reliable method of checking the results of serum therapy.

The statistics for the Hospital showed that, though the case mortality for 1925 was 3.14% as compared with 1.99% for 1926, there was no appreciable difference/

difference between the incidence of the well-known complications of the disease during the two years in question.

In estimating the therapeutic value of serum therapy in Scarlet fever the salient points which I have chosen for consideration coincide closely with those taken up by previous workers, and it is upon these that we must judge the resultant effects of such a treatment.

The present day problem of Scarlet fever is chiefly one of late morbidity and so any therapeutic measure directed against this disease must, to justify its continued application, have a beneficial action upon the associated complications developing during convalescence.

Certain effects such as

1. Rapid fall of temperature and pulse rate to normal
2. Amelioration of Nervous Symptoms.
3. Blanching of exanthem.
4. Modification or absence of desquamation.
5. Serum reactions

are agreed upon by all observers.

The first three points entail a prompt neutralisation of the specific toxæmia of the disease - which property the Scarlet fever streptococcus anti-toxic serum has been shown repeatedly to possess.

With regard to the question of serum reactions it/

it is the unanimous opinion that, with the most modern methods of concentrating the sera in question, these reactions are cut down considerably in frequency, and their severity much reduced as compared with the undesirable effects of the older, unconcentrated preparations.

My own results, with regard to the above features, correspond very closely to those hitherto recorded except that the fall in temperature following the administration of serum, though very dramatic in many instances, was not so marked as in the hands of some observers.

Cushing³² states that:-

"The most certain effect of serum, if given early (during the first week), is to produce a marked fall of temperature. This is a characteristic, uniform reaction which occurs in all cases."

We have thus seen that the specific antitoxic serum is a powerful agent in counteracting the toxaemic phase of the disease and we now turn our attention to its effects upon the septic aspect of Scarlet fever.

In this respect we deal with the questions of:-

1. Effect upon complications.
2. Duration of stay in Hospital.
3. Mortality.

The views of various workers are not quite so agreed upon these points, some claiming rather extravagant/

extravagant results from the use of specific antitoxic serum in abolishing complications and sequelae and in the cutting down of mortality rate and the customary quarantine period.

However, it seems to be the general opinion amongst the most recent workers that such a serum, while it has little or no direct antagonistic action against the septic element of Scarlet fever, it nevertheless is a valuable therapeutic measure in attacking that phase of the disease indirectly by freeing the patient of the toxaemia and hence placing him or her in a better position to fight the sepsis complicating the original infection.

With regard to the question of sera containing antibacterial as well as antitoxic properties, we expect such preparations to have a more direct action in combating the organismal infection as well as their specific toxins.

Thus, though at present we do not look for a complete abolition of the complications associated with Scarlet fever as a result of treatment with specific antitoxic serum, however early given and even in large doses, we do expect a definite reduction in the incidence and severity of such complications.

The tables bearing the statistics of the three hundred and sixty-five cases treated with serum and a similar number of non-serum treated cases corroborate the/

the truth of the above statement.

The most favourable results were obtained with cases treated with serum during the first day of disease, while with regard to the cases coming under observation on the fourth day, making allowance for the small number treated and the more severe type of case, the facts suggest that, with each day of delay in the administration of serum, the beneficial effects are considerably lessened.

It is with special interest that we note the effect of specific serum therapy in the prevention of Nephritis, - a complication which is generally regarded as due to the specific toxæmia of the disease rather than as a manifestation of post Scarlatinal sepsis.

Amongst the three hundred and forty-four cases of simple Scarlet fever treated with serum during the first three days of disease there was only one case of an extremely mild form of Nephritis, while in a similar number of control cases there were three definite clinical cases of that complication.

Resulting from this diminution in incidence and severity of complications it is only natural that the period of Hospitalisation should be likewise reduced, giving an economic advantage and a relief to the strain upon the accommodation in Fever Hospitals which cases of Scarlet fever showing complications entail.

In/

In respect of the cutting down of the customary quarantine period of four weeks for uncomplicated cases of Scarlet fever it was not considered advisable to further reduce this period in serum treated cases.

The effect upon case mortality has previously been alluded to and, as explained, in districts where this figure is already very low, there has been little dramatic change, though it is to be expected that the results of serum therapy are in all cases favourable through its power of counteracting the specific toxæmia and reducing the incidence and severity of complications.

In countries where the case mortality from Scarlet fever is still high, more definite information in this respect would be obtained.

The problem of relapses and second attacks being rendered more prevalent has already been discussed and, as pointed out, the percentage of relapses was not found to be increased beyond normal limits.

Second attacks of Scarlet fever, though rare, occur quite apart from serum therapy.

I have had, as yet, no second attacks amongst the cases treated with antitoxic serum.

The question of dosage has given considerable trouble to all investigators and the difficulties attached to the standardisation and titration of Scarlet fever antitoxic sera are largely responsible for/

for this problem.

The cases of Simple Scarlet fever in the anti-toxin series were approximately all of the same severity and each received an injection of 10 ccm. of the specific antitoxic serum.

The method of giving a uniform dose to a large number of cases was adopted in order to be able to judge from the effects obtained whether this dose was sufficient for such a type of case.

The results show that for the average case of simple Scarlet fever this dose, which contains approximately enough antitoxin to neutralise 500,000 skin test doses of toxin, constitutes an adequate therapeutic dose.

However, each case must be judged upon its own merits and when thought advisable that dose should be increased.

In definite cases of Septic Scarlet fever the effects of a specific antitoxin are of an indirect character with reference to the septic phase of the disease.

If administered while the toxic element still manifests itself it relieves the patient of the specific toxæmia and so improves his condition by increasing his powers of resistance to overcome the septic infection.

If/

If treatment be delayed till after rash and other signs and symptoms of the toxaemia have gone, there is little likelihood of the specific antitoxic serum having any influence upon the clinical course of the disease.

In this type of case the specific serum therapy was combined with the giving of a polyvalent anti-streptococcal serum whereby it was hoped to attack simultaneously the two aspects of the infection.

The number of cases so treated was extremely small, but the results seemed to justify its application and gave promise of a favourable line of attack against this type of Scarlet fever which is particularly troublesome from a therapeutic point of view.

In the toxic type of disease the results in the two cases treated were very satisfactory.

It is essential to get the patients early under observation while they are yet capable of responding to the treatment and to give the specific antitoxic serum preferably by the intravenous route, repeating the dose should definite improvement in the patient's condition not manifest itself within twelve hours of the first administration.

C O N C L U S I O N S .

From a study of three hundred and sixty-five cases of Simple Scarlet fever, treated by intramuscular injection of 10 ccm. of concentrated Scarlet fever streptococcus antitoxic serum, the following are the conclusions:-

1. The administration of antitoxic serum within the first three days of disease produces a very favourable effect upon the specific toxæmia of the disease as manifested by:-
 - (a) A more rapid return to normal of temperature and pulse curves.
 - (b) Marked diminution of nervous symptoms.
 - (c) Definite blanching of the rash which, in 60% of the cases treated, entirely disappeared within 24 hours.
2. For cases of simple Scarlet fever of average severity an efficient therapeutic dose should contain enough antitoxin to neutralise 500,000 skin test doses of a standard Scarlet fever toxin, i.e. 5,000 units of antitoxin.
3. This should be regarded as the minimum therapeutic dose which ought to be increased according to the severity of the case.

4. The methods at present in use of standardising such a serum present considerable difficulties.
5. The full therapeutic dose should be given at the earliest possible moment. When thus given the results are, in most cases, strikingly favourable.
6. The use of a reliable concentrated serum produces fewer and less severe reactions than an unconcentrated preparation.
7. When given within the first three days of disease it cuts short the course of the disease, lessens the incidence and reduces the severity of complications.
8. The administration of serum even on the first day of disease is not an absolute safeguard against the development of complications of the septic type.
9. The therapeutic efficacy of the serum diminishes with each day of delay in its administration and beyond the third day of disease it appears to have little or no effect in influencing the incidence of subsequent complications.
10. Until more definite data are available it does not seem advisable to further reduce the usual quarantine period of Scarlet fever patients treated with specific antitoxic serum, but the total/

total period of hospitalisation of such patients is reduced owing to the serum therapy reducing the incidence and severity of complications.

11. Antitoxin treatment of Scarlet fever does not appear to increase the incidence of relapses beyond normal limits.
12. A further period of study is required to determine what influence serum therapy has upon the prevalence of second attacks of the disease.
13. The case mortality from Simple Scarlet fever is so low at present that it renders it difficult to determine the effects of serum therapy in further reducing this figure.
14. In cases of septic Scarlet fever the specific antitoxic serum only indirectly benefits the initial septic complications by curing the toxaemia.
15. There is reason to believe that the treatment of Septic Scarlet fever by a combination of specific antitoxic serum and polyvalent antistreptococcal serum cuts short the course of the disease and lessens the liability to the development of subsequent septic complications.

16. Specific antitoxic serum, if given early and in large doses, is an extremely efficacious treatment for cases of Toxic Scarlet fever.
 17. The intravenous method of administration is more advantageous to toxic cases than the intramuscular route as it ensures a more rapid maximum concentration of antitoxin in the patient's circulation.
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B I B L I O G R A P H Y.

1. Zingher, A. J.A.M.A. Vol.83, p.432. Aug. 9th
1924.
2. Tunnicliff, Ruth. J.A.M.A. Vol.74, p.1386.
May 15th, 1920.
3. Bliss, W.P. Bull. J. Hopkins' Hosp. 31: 173.
May 1920.
4. Gordon, M.H. B.M.J. Vol.1. p.632. Apr.10th 1921.
5. Dochez, A.R. & Sherman, Lillian. Proc. Soc.
Exper. Biol. & Med. 21: 184.
Jan. 1924.
6. Dick, G.F. & G.H. J.A.M.A. Vol.82: p.265.
Jan. 26th, 1924.
7. Zingher, A. J.A.M.A. Vol.83: p.432. Aug.9th
1924.
8. Klein. L.G.B. Reports 1886-7. Vol.16:
Supplement Appendix B. p.367.
9. Marmorek, A. Ann. de L'Inst. Pasteur. IX: 593:
1895.
10. Moser, P. Wien. Klin. Woch. XV: 1053: 1902.
11. Schick Pfaundler & Schlossmann. "Diseases
of Children". Vol.II, p.315.
12. Goodall, E.W. Med. Annual 1909.
13. Compston, H. B.M.J. Vol I: p.1291. May 30th 1908.
14. Ker, Claud B. Infect. Dis. 1920.
15. Harries, E.H.R. Public Health. Jan. 1926.

16. Weisbecker. Ztschr. f. Klin. Med. XXXII: 188:
1897.
17. Bernbaum, B. Journ. Mich. Med. Soc. XXI: 249:
1922.
18. Birkhaug, K.E. Bull. J. Hopkins' Hosp. Vol.36:
p. 134: Feb. 2nd 1925.
19. Dochez, A.R. & Sherman, Lillian. J.A.M.A.
Vol.82: p.542. Feb. 16th 1924.
20. Thenebe, C.L. Boston Med. & Surg. Journ.
May 14th and Sept. 10th 1925.
21. Blake, F.G. & Trask, J.D. Boston Med. & Surg.
Journ. p.659. Oct. 8th 1925.
22. Blake, F.G., Trask J.D. & Lynch J.F. J.A.M.A.
Vol.82: p.712. 1924.
23. Blake, F.G. Boston Med. & Surg. Journ.
CXCI: 43: 1924.
Trans.Assn.Am. Phys.39: 141: 1924.
24. Park, W.H. J.A.M.A. Vol.85. p.1180. Oct 17th
1925.
25. Robb Gardner A. B.M.J. p.11: Jan. 2nd 1926.
26. Dick G.F. & G.H. J.A.M.A. Vol.82: p.1246.
Apr. 19th 1924.
27. Dick G.F. & G.H. J.A.M.A. Vol.84: p.803. 1925.
28. Dick G.F. & G.H. J.A.M.A. Vol.85: p.1693:
Nov. 28th 1925.
29. Ferry N.S. Bernbaum B. & Crissman H.C. -
Therapeutic Gazette. Apr. 1925.
30. Williams Anna W. Amer. Journ. Pub. Health
Vol.15: p.129: Feb. 1925.
31. /

31. Anderson, J.F. & Leonard G.F. - Amer. Journ.
Med. Science, p.334. Sept. 1926.
32. Cushing H.B. Canadian Med. Assoc. Journ.
p.937. Aug. 1926.
33. Benson W.T. & Maciver D.P. Edin. Med. Journ.
p.701. Dec. 1926.
34. Gordon J.E. J.A.M.A. Vol.88: p.382: Feb. 5th
1927.
35. Bie, V., Larsen A. & Andersen M.S. - Acta. Med.
Scand. P.238. Apr. 30th 1927.
36. Discussion by Roy. Med. Soc. B.M.J. p.424.
March 5th 1927.
37. Wadsworth A.B., Kirkbride Mary B. & Wheeler,
Mary W. J.A.M.A. Vol.87.
Aug. 28th 1926.
38. Blake F.G. & Trask J.D. New York State Med.
Journ. 25: 1093: Dec. 15th 1925.
